Amendments to the Specification

Please replace the paragraph beginning on page 6 at line 3, with the following amended paragraph:

"Peptide" or "protein": According to the present invention, a "peptide" or "protein" comprises a string of at least three amino acids linked together by peptide bonds. The terms "protein" and "peptide" may be used interchangeably. Peptide may refer to an individual peptide or a collection of peptides. Inventive peptides preferably contain only natural amino acids, although non-natural amino acids (*i.e.*, compounds that do not occur in nature but that can be incorporated into a polypeptide chain~~; see, for example, http://www.cco.caltech.edu/~dadgrp/Unnatstruct.gif, which displays structures of non-natural amino acids that have been successfully incorporated into functional ion channels~~) and/or amino acid analogs as are known in the art may alternatively be employed. Also, one or more of the amino acids in an inventive peptide may be modified, for example, by the addition of a chemical entity such as a carbohydrate group, a phosphate group, a farnesyl group, an isofarnesyl group, a fatty acid group, a linker for conjugation, functionalization, or other modification, *etc.* In a preferred embodiment, the modifications of the peptide lead to a more stable peptide (*e.g.*, greater half-life *in vivo*). These modifications may include cyclization of the peptide, the incorporation of D-amino acids, *etc.* None of the modifications should substantially interfere with the desired biological activity of the peptide.

Please insert the following paragraph on page 7 after line 20, "**Brief Description of the Drawing**":

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Please delete the paragraph, beginning at page 9 at line 12, which begins "*Figure 5* shows a Kaplan-Meier . . . ."

Please replace the paragraph, beginning on page 9 at line 15, with the following amended paragraph:

Figure ~~6~~ 5 shows ~~the data obtained from the top 22 genes with *Wnt5a* at the top of the list. The figure also show~~ a diagram of the *Wnt5a* and *Wnt1* signaling pathways.

Please replace the paragraph, beginning on page 9 at line 17, with the following amended paragraph:

Figure ~~7~~ 6 shows the data from real time PCR analysis of three cell lines, one with low *Wnt5a* expression (which scored as having low expression in the gene chip analysis), one with high *Wnt5a* expression (which scored as having high expression in the gene chip analysis), and one with intermediate *Wnt5a* expression, an originally low scoring cell line which had been transfected with a vector designed to express *Wnt5a.* The patent and transfected cell line were also analyzed for WNT5A protein abundance using Western blot analysis and immunohistochemical staining.

Please replace the paragraph, beginning on page 10 at line 1, with the following amended paragraph:

Figure ~~8~~ 7 shows the dramatic changes in cell morphology and cytoskeletal organization upon transfection of the parental cell line with a vector driving *Wnt5a* expression. The parental cell line is spindle shaped with few points of attachment to the culture plate and disorganized actin filaments. The transfectants are broader and flatter with many extensions and highly polarlized actin filaments.

Please replace the paragraph, beginning on page 10 at line 6, with the following amended paragraph:

Figure ~~9~~ 8 shows the results of experiments done to look at possible cross talk between the *Wnt5a* and *Wnt1* pathways. Beta-catenin was localized to the cytoplasm indicating that the *Wnt1* pathway is not active. The downstream target of *Wnt5a*, protein kinase C, was also observed to be phosphorylated, especially the mu and alpha/beta isoforms, indicating that the expected *Wnt5a* pathway is active.

Please replace the paragraph, beginning on page 10 at line 11, with the following amended paragraph:

Figure ~~10~~ 9 shows scratch assay and Boyden chamber assay results for the parent cell line as well as the transfected cell line. The results from these two standard assays show that increased cell movement and invasiveness correlate with increased *Wnt5a* expression.

Please replace the paragraph, beginning on page 10 at line 14, with the following amended paragraph:

Figure ~~11~~ 10 shows that the transition from low to high *Wnt5a* expression is not associated with increasing amounts of the G protein coupled receptor, frizzled 5 (fzd5). Also shown are results indicating that an antibody to fzd5 can attenuate or reverse the phenotype that increased *Wnt5a* would normally produce.

Please replace the paragraph beginning on page 14 at line21, with the following amended paragraph:

The sequence of the mRNA of *Homo sapiens* wingless MMTV integration site family, member 5a (*Wnt5a*) is shown below:

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  1 attaattctg gctccacttg ttgctcggcc caggttgggg agaggacgga gggtggccgc
 61 agcgggttcc tgagtgaatt acccaggagg gactgagcac agcaccaact agagaggggt
121 caggggggtgc gggactcgag cgagcaggaa ggaggcagcg cctggcacca gggctttgac
181 tcaacagaat tgagacacgt ttgtaatcgc tggcgtgccc cgcgcacagg atcccagcga
241 aaatcagatt tcctggtgag gttgcgtggg tggattaatt tggaaaaaga aactgcctat
301 atcttgccat caaaaaactc acggaggaga agcgcagtca atcaacagta aacttaagag
361 acccccgatg ctcccctggt ttaacttgta tgcttgaaaa ttatctgaga gggaataaac
421 atcttttcct tcttccctct ccagaagtcc attggaatat taagcccagg agttgctttg
481 gggatggctg gaagtgcaat gtcttccaag ttcttcctag tggctttggc catatttttc
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 541 tccttcgccc aggttgtaat tgaagccaat tcttggtggt cgctaggtat gaataaccct
 601 gttcagatgt cagaagtata tattatagga gcacagcctc tctgcagcca actggcagga
 661 ctttctcaag gacagaagaa actgtgccac ttgtatcagg accacatgca gtacatcgga
 721 gaaggcgcga agacaggcat caaagaatgc cagtatcaat tccgacatcg acggtggaac
 781 tgcagcactg tggataacac ctctgttttt ggcagggtga tgcagatagg cagccgcgag
 841 acggccttca catacgccgt gagcgcagca ggggtggtga acgccatgag ccgggcgtgc
 901 cgcgagggcg agctgtccac ctgcggctgc agccgcgccg cgcgccccaa ggacctgccg
 961 cgggactggc tctggggcgg ctgcggcgac aacatcgact atggctaccg ctttgccaag
1021 gagttcgtgg acgcccgcga gcgggagcgc atccacgcca agggctccta cgagagtgct
1081 cgcatcctca tgaacctgca caacaacgag gccggccgca ggacggtgta caacctggct
1141 gatgtggcct gcaagtgcca tggggtgtcc ggctcatgta gcctgaagac atgctggctg
1201 cagctggcag acttccgcaa ggtgggtgat gccctgaagg agaagtacga cagcgcggcg
1261 gccatgcggc tcaacagccg gggcaagttg gtacaggtca acagccgctt caactcgccc
1321 accacacaag acctggtcta catcgacccc agccctgact actgcgtgcg caatgagagc
1381 accggctcgc tgggcacgca gggccgcctg tgcaacaaga cgtcggaggg catggatggc
1441 tgcgagctca tgtgctgcgg ccgtgggtac gaccagttca agaccgtgca gacggagcgc
1501 tgccactgca agttccactg gtgctgctac gtcaagtgca agaagtgcac ggagatcgtg
1561 gaccagtttg tgtgcaagta gtgggtgcca cccagcactc agccccgctc ccaggacccg
1621 cttatttata gaaagtacag tgattctggt ttttggtttt tagaaatatt ttttatttct
1681 ccccaagaat tgcaaccgga accatttttt ttcctgttac catctaagaa ctctgtggtt
1741 tattattaat attataatta ttatttggca ataatggggg tgggaaccac gaaaaatatt
1801 tattttgtgg atctttgaaa aggtaataca agacttcttt tggatagtat agaatgaagg
1861 gggaaataac acatacccta acttagctgt gtgggacatg gtacacatcc agaaggtaaa
1921 gaaatacatt ttctttttct caaatatgcc atcatatggg atgggtaggt tccagttgaa
1981 agagggtggt agaaatctat tcacaattca gcttctatga ccaaaatgag ttgtaaattc
2041 tctggtgcaa gataaaaggt cttgggaaaa caaaacaaaa caaaacaaac ctcccttccc
2101 cagcagggct gctagcttgc tttctgcatt ttcaaaatga taatttacaa tggaaggaca
2161 agaatgtcat attctcaagg aaaaaaggta tatcacatgt ctcattctcc tcaaatattc
2221 catttgcaga cagaccgtca tattctaata gctcatgaaa tttgggcagc agggaggaaa
2281 gtccccagaa attaaaaaat ttaaaactct tatgtcaaga tgttgatttg aagctgttat
2341 aagaattggg attccagatt tgtaaaaaga cccccaatga ttctggacac tagatttttt
2401 gtttggggag gttggcttga acataaatga aatatcctgt attttcttag ggatacttgg
2461 ttagtaaatt ataatagtag aaataataca tgaatcccat tcacaggttt ctcagcccaa
2521 gcaacaaggt aattgcgtgc cattcagcac tgcaccagag cagacaacct atttgaggaa
2581 aaacagtgaa atccaccttc ctcttcacac tgagccctct ctgattcctc cgtgttgtga
2641 tgtgatgctg gccacgtttc caaacggcag ctccactggg tccccctttgg ttgtaggaca
2701 ggaaatgaaa cattaggagc tctgcttgga aaacagttca ctacttaggg atttttgttt
2761 cctaaaactt ttattttgag gagcagtagt tttctatgtt ttaatgacag aacttggcta
2821 atggaattca cagaggtgtt gcagcgtatc actgttatga tcctgtgttt agattatcca
2881 ctcatgcttc tcctattgta ctgcaggtgt accttaaaac tgttcccagt gtacttgaac
2941 agttgcattt ataaggggggg aaatgtggtt taatggtgcc tgatatctca aagtcttttg
3001 tacataacat atatatatat atacatatat ataaatataa atataaatat atctcattgc
3061 agccagtgat ttagatttac agcttactct ggggttatct ctctgtctag agcattgttg
3121 tccttcactg cagtccagtt gggattattc caaaagtttt ttgagtcttg agcttgggct
3181 gtggccccgc tgtgatcata ccctgagcac gacgaagcaa cctcgtttct gaggaagaag
3241 cttgagttct gactcactga aatgcgtgtt gggttgaaga tatcttttt tcttttctgc
3301 ctcacccctt tgtctccaac ctccatttct gttcactttg tggagagggc attacttgtt
3361 cgttatagac atggacgtta agagatattc aaaactcaga agcatcagca atgtttctct
3421 tttcttagtt cattctgcag aatggaaacc catgcctatt agaaatgaca gtacttatta
3481 attgagtccc taaggaatat tcagcccact acatagatag ctttttttttt ttttttttt
3541 ttttaataag gacacctctt tccaaacagg ccatcaaata tgttcttatc tcagacttac
3601 gttgttttaa aagtttggaa agatacacat cttttcatac ccccccttag gaggttgggc
3661 tttcatatca cctcagccaa ctgtggctct taatttattg cataatgata tccacatcag
3721 ccaactgtgg ctctttaatt tattgcataa tgatattcac atcccctcag ttgcagtgaa
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3781 ttgtgagcaa aagatcttga aagcaaaaag cactaattag tttaaaatgt cacttttttg
3841 gtttttatta tacaaaaacc atgaagtact ttttttattt gctaaatcag attgttcctt
3901 tttagtgact catgtttatg aagagagttg agtttaacaa tcctagcttt taaaagaaac
3961 tatttaatgt aaaatattct acatgtcatt cagatattat gtatatcttc tagcctttat
4021 tctgtacttt taatgtacat atttctgtct tgcgtgattt gtatatttca ctggtttaaa
4081 aaacaaacat cgaaaggctt attccaaatg gaag
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(Seq. ID No.: 2)

Please replace the paragraph, beginning on page 20 at line 11, with the following amended paragraph:

In other embodiments, agents may be screened for their ability to inhibit or knock out the *Wnt5a* pathway as shown in Figure ~~6~~ 5. In one embodiment, agents may be screened for their ability to block the binding of WNT5A to its receptor, frizzled 5. An agent able to block this binding interaction could possibly attenuate or reverse the phenotypes that increased WNT5A would normally produce, such as increased cell movement an invasiveness.

Please replace the paragraph beginning on page 30 at line 22, with the following amended paragraph:

Cultured cells were collected and mRNA isolated as described (Khan *et al.* "DNA Microarray technology: the anticipated impact on the study of human disease" *Biochim. Biophys. Acta* 1423:17-28, 1999; ~~www.nhgri.nih.gov//DIR/microarray;~~ each of which is incorporated herein by reference). Samples underwent a series of controls for quality of mRNA, labeling and hybridization, as well as sample integrity (including genotyping DNA from all samples with five dinucleotide markers from four different chromosomes to insure individuality). The entire coding sequence of the p16 gene and exon 3 of the ß-catenin genes was sequenced to assess the mutation status of all available samples (see Supplementary Information). The biopsy ~~tumour~~ tumor specimens used in this study were obtained with Institutional Review Board approval and clinical information is provided in the Supplementary Information. Biopsies were debrided, dissected into small pieces and frozen in liquid nitrogen. Frozen specimens were immediately placed into TRIzol Reagent (Gibco BRL), homogenized and mRNA isolated as described (Khan *et al.* "DNA Microarray Technology: The Anticipated Impact on the Study of Human Disease" *Biochim. Biophys. Acta* 1423:17-28, 1999; ~~www.nhgri.nih.gov/DIR/microarray;~~ each of which is incorporated herein by reference).

Please replace the paragraph beginning on page 31 at line 16, with the following amended paragraph:

The 8,150 human cDNAs used in this study were obtained under a Cooperative Research and Development Agreement with Research Genetics and 6,912 were verified by sequence. This set of cDNAs is part of a larger collection (Khan *et al.* "Gene expression profiling of alveolar rhabdomyosarcoma with cDNA microarrays" *Cancer Res.* 58:5009-5013, 1998; Duggan *et al.* "Expression profiling using cDNA microarrays" *Nature Genet.* 21:10-14, 1999; ~~www.nhgri.nih.gov/DIR/microarray;~~ each of which is incorporated herein by reference). On the basis of the Unigene build of 9 March 2000 ~~(http://www.ncbi.nlm.nih.gov/UniGene/build.html)~~, the 8,150 cDNAs represent 6,971 unique genes in this melanoma array. All clones were confirmed by resequencing if necessary. Microarrays were hybridized, scanned and image analysis performed as described (Khan *et al.* "Gene expression profiling of alveolar rhabdomyosarcoma with cDNA microarrays" *Cancer Res.* 58:5009-5013, 1998; Khan *et al.* "DNA Microarray technology: the anticipated impact on the study of human disease" *Biochim. Biophys. Acta* 1423:17-28, 1999; ~~www.nhgri.nih.gov/DIR/microarray;~~ each of which is incorporated herein by reference). The raw data from the microarray is shown in Appendix A, a Microsoft Excel Worksheet, which has been included on a CD-ROM submitted with this application and is incorporated herein by reference.

Please replace the paragraph, beginning on page 36 at line 12, with the following amended paragraph:

Hierarchical clustering of the 31 melanoma samples was performed, resulting in a dendrogram (Fig. ~~1b~~ 1). Although the dendrogram gives insights about the similarity and relatedness among samples, it does not indicate robustness to variability associated with the assay sampling, etc. In order to draw valid conclusions about the clustering structure present in the data, it is necessary to investigate how variability affects the results of the cluster analysis. To this end, we developed and implemented a method that determines the reproducibility of given levels of cluster structure within the dendrogram under the condition of added noise. The method is described below.

Please replace the paragraph, beginning on page 41 at line 12, with the following amended paragraph:

~~The data used in the survival analysis are shown in Figure 1.~~ A total of 15 cases were included in the analysis, 10 from Group A and 5 from Group B. Survival/follow-up times were rounded to the nearest quarter year. A Kaplan-Meier survival plot was created and log-rank test performed. No statistically significant association between group and survival was found (p=0.135).

Please replace the paragraph, beginning on page 51 at line 11, with the following amended paragraph:

Wnt5a scored very high out of all the marker genes analyzed in the ability to discriminate between highly invasive malignant melanoma and less invasive melanoma. Melanoma samples with high levels of *Wnt5a* expression were more aggressive tumors than those with lower levels of *Wnt5a* expression. Figure ~~6~~ 2B shows the top 22 genes selected for their ability to classify highly invasive malignant melanoma from less invasive melanoma. *Wnt5a* is at the tope of the list of these marker genes.

Please replace the paragraph, beginning on page 52 at line 1, with the following amended paragraph:

Figure ~~6~~ 5 also shows *Wnt5a*'s expected signaling pathway in contrast to the *Wnt1* pathway. *Wnt1* is known to be transforming; however, its proximal methods of signaling are very difference from those of *Wnt5a*. In some studies, researchers have observed that the two pathways seem to oppose each other in terms of downstream effects. In the *Wnt5a* pathway, the first transduction of the *Wnt5a* signal is accomplished through the interaction of *Wnt5a* with a G protein-coupled receptor, frizzled 5 (FZD5). The signal is subsequently transduced through the PLC/IP3/DAG/PKC pathways. The *Wnt5a* signal eventually leads to integrin interactions, cytoskeletal effects, and other cellular effects.

Please replace the paragraph, beginning on page 52 at line 9, with the following amended paragraph:

Low level expression of *Wnt5a* in the cluster of 19 melanomas was verified by real time PCR. Data for the samples WM-1791C and UACC-1273 are shown in Figure ~~7~~ 6A. The real time PCR results show that there is much more *Wnt5a* transcript in cell line WM-1791C, which originally was scored as having high level expression of *Wnt5a* by gene chip analysis, than in UACC-1273, which was originally scored as having low level expression. Vectors used to express higher levels of Wnt5a in cells that normally express low levels were developed using standard techniques to see if the phenotype of less aggressive samples expressing low levels of Wnt5a could be changed. A derivative of UACC-1273, a transfectant 4-3, which had been transfected with this vector, shows an intermediate level of *Wnt5a* expression in the real time PCR analysis. The increase in *Wnt5a* expression carries over in WNT5A protein abundance as shown by Western blot and by immunohistochemical staining (nuclei staining blue, WNT5A staining red) (Figure ~~7~~ 6B and 6C).

Please replace the paragraph, beginning on page 52 at line 21, with the following amended paragraph:

In terms of morphology, cell lines with originally low levels of *Wnt5a* expression showed dramatic changes in morphology and cytoskeletal organization when stably transfected with a vector driving *Wnt5a* expression. The parental line, UACC-1273, is spindle shaped with few points of attachment to the culture plate and disorganized actin filaments (Figure ~~8~~ 7). The transfectants are broader and flatter with many extensions and highly polarized actin filaments.

Please replace the paragraph, beginning on page 52 at line 3, with the following amended paragraph:

In order to determine whether there was cross talk between the *Wnt5a* and *Wnt1* pathways, an assay looking at beta-catenin was used. When *Wnt1* signaling is active, beta-catenin is localized to the nucleus. In Figure ~~9~~ 8A, antibody staining for beta-catenin shows that the beta-catenin is localized in the cytoplasm and not concentrated in the nucleus. Therefore, no cross talk between the two pathways seems to be occurring.

Please replace the paragraph, beginning on page 52 at line 8, with the following amended

paragraph:

Protein kinase C (PKC), a downstream target likely to be modulated by *Wnt5a*, was also looked at. *Wnt5a* modulates PKC activity by phosphorylation of some or all of the PKC isoforms and not by alteration of PKC transcript levels. As can be seen in Figure 8 ~~9~~, increased phosphorylated PKC is produced in the transfectants expressing significant levels of the *Wnt5a* transcript, as expected. The isoforms must frequently phosphorylated are mu and alpha/beta. This is further evidence that one is looking at the exptected *Wnt5a* pathway. PKC is one of the central hubs of signal transduction, and pathways leading to many types of cellular action incuding proliferation, cytoskeletal organization, and cell movement are known.

Please replace the paragraph, beginning on page 53 at line 17, with the following amended paragraph:

Increased cell movement and invasiveness were also found to correlate with increased *Wnt5a* expression in a scratch assay and a Boyden chamber assay. Transfectants expressing increased levels of *Wnt5a* show increased competence in filling in open gaps on a cell culture dish when compared to cells of the parent cell line (Figure ~~10~~ 9). Increased phosphorylated PKC was found to correlate with increasing cell invasiveness as measured by a standard test for invasiveness, the Boyden chamber assay.

Please replace the paragraph, beginning on page 53 at line 23, with the following amended paragraph:

The first transduction of the *Wnt5a* signal is accomplished through interaction with a G protein coupled, seven transmembrane receptor, frizzled 5. The various cell lines tested show varying native levels of fzd5 transcript. In the cell line, UACC-1273, the transition from low to high *Wnt5a* expression is not associated with increasing amounts of the receptor. The use of an antibody to fzd5 prevents it from responding to *Wnt5a* and thereby attenuates or reverses the phenotypes that increased *Wnt5a* would normally produce. This is shown in the decreased level of phosphorylated PKC upon treatment with the anti-fzd antibody and in the decreased invasiveness of *Wnt5a* transfectants treated with the ant-fzd antibody (Figure 10).